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**SECOND DECLARATION  
UNDER RULE 132**

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First Inventor	MONTEIL
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Examiner	Reyes, Hector M.
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S I R:

I, Denis DANVY, residing at 6A rue Haëmers, 76190 Yvetot (France),

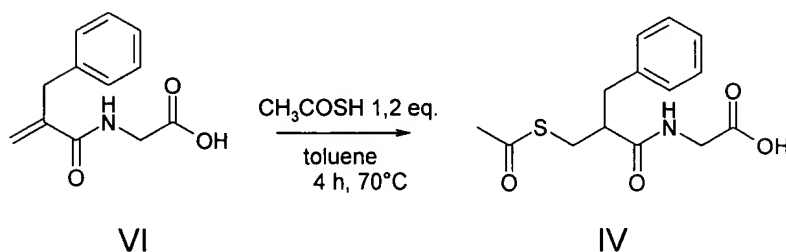
Declare and say :

1. I am a citizen of France. I am one of the co-inventors of the above identified case and having read the present specification and the prior art cited against this patent application, I am very familiar with the subject matter of this case.

2. In response to the outstanding prior art rejections based on the alleged obviousness of the above-identified application, I wish to outline and submit the following comments:

In order to compare the coupling reaction with ester derivatives of the invention with a similar reaction with acid derivatives as taught by Greenberg et al U.S. Patent Nos. 4,401,677 and 4,474,799 (hereinafter collectively "Greenberg et al"), the following experiments have been conducted :

a. The acid reaction (as per Greenberg et al)



In a vessel, 26.53 g of the acrylamid acid derivative (VI) are dissolved in 40 mL of toluene. 11.3 mL of S-thioacetic acid is added. The reaction mixture is mixed and heated at 70°C for 4 hours. After removal of the solvents, the obtained product is stirred with diethyl oxide and further concentrated. This step is renewed one more time. The obtained product is mixed with 200 mL of diethyl oxide, cooled and mixed for 2 hours. The precipitated product is filtered, washed with diisopropyl oxide and dried under reduced pressure at 50°C on phosphorus pentaoxide.

The white obtained precipitated solid weights  $m_1 = 15.54$  g and is 94.7 % pure (HPLC). The filtrated liquid is concentrated, stirred with 200 mL of diethyl oxide, cooled and stirred for 2 hours. The precipitated product is filtered, washed with diethyl oxide and dried under reduced pressure at 50°C on phosphorus pentaoxide. The obtained solid weights  $m_2 = 7.46$  g and is 90.2% pure (HPLC). Both fractions are combined. The obtained combined product weights :  $m_1 + m_2 = 22.96$  g.

The product is purified by dissolving in 200 mL of isopropyl alcohol, followed by addition of 8,9 mL of cyclohexylamine. The solution is stirred until solidified, then stirred, filtered and washed with a mixture of diethyl oxide and 2-propanol (50/50). The cyclohexylamine salt is dissolved in ethyl acetate and water. An aqueous solution of hydrochloride acid 1N is added until pH = 1, so as to form the free acid. The organic phase is washed two times with an aqueous solution of hydrochloride acid 1N, then two times with water. The organic phase is dried on magnesium sulphate, filtered and concentrated. The obtained white product is dried under reduced pressure at 50°C on phosphorus pentaoxide.

The purified product weights 13 g (theoretical mass = 35.74 g), yield = 36 %.

The following analysis have been carried out to characterize the product:

RMN  $^1\text{H}$  ( $\text{CDCl}_3$ ) :

7,28 à 7,16 (large, 5H, H aromatic); 5,93 (large, 1H, NH); 3,98 (dd, 1H, NH-CH<sub>2</sub>,  $J_{\text{NH-CH}_2} = 5\text{Hz}$ ,  $J_{\text{CH}_2} = 18\text{Hz}$ ) ; 3,91 (dd, 1H, NH-CH<sub>2</sub>,  $J_{\text{NH-CH}_2} = 3\text{Hz}$ ,  $J_{\text{CH}_2} = 18\text{Hz}$ ) ; 3,12 à 2,89 (large, 4H, S-CH<sub>2</sub> et CH<sub>2</sub>-Ph) ; 2,78 à 2,58 (large, 1H, CH) ; 2,34 (s, 3H, CH<sub>3</sub>) ; 3,2 à 2,5 (sl, 1H, OH)

HPLC :

Column : Lichrospher ODS C18, 250 x 4.0 mm, porosity : 5  $\mu\text{m}$

Eluent : 60 % water and 40 % acetonitril

Detection : UV at 210 nm

Injection : 10  $\mu\text{L}$  of a solution at approximately 1 mg in 2 mL eluent

Results : TR : 5,12 minutes. Purity = 97.1 %

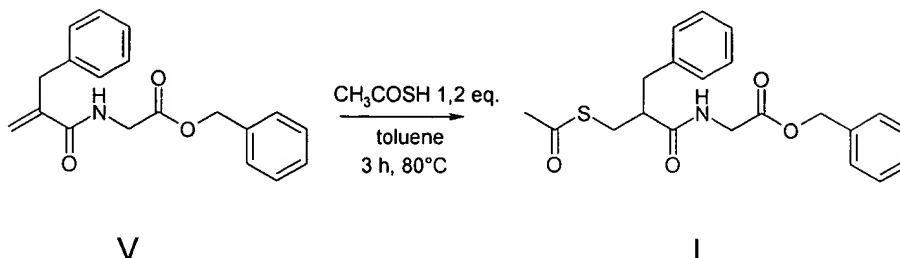
(Percentages are given as surface percentages)

Melting point : 105°C

IR : (KBr)

$\nu$  (in  $\text{cm}^{-1}$ ) = 3320 (F,  $\nu$  NH) ; 1727 (F,  $\nu$  C=O acid) ; 1691 (F,  $\nu$  C=O acetyl) ; 1647 (F,  $\nu$  C=O amid)

b. The ester reaction according to the invention



This reaction is performed in accordance with the examples given in the specification (in particular, example 1).

Yield: 75 %.

Purity of the obtained product = 99 %.

3. Comparing the results of reactions a and b from Section 2, the present ester reaction allows higher yield and purity of the obtained product, namely in this experiment, 75% yield and 99% purity vs. 36% yield and 97% purity.

4. Additionally, the process of the invention is particularly advantageous in that it can be easily implemented, in particular in industrial scale. This is, in particular, because the starting product is easily purified, for the reason below:

In accordance with the present invention, the starting product of formula (V) easily crystallizes, in a mixture of isopropanol and isopropyl ether (see examples 1 and 2).

5. The present method is distinguishable from Greenberg et al. First, it would not have been obvious to substitute an ester reaction, such as in the present invention, in place of the prior art (Greenberg et al) acid reaction as the conventional thinking was that an ester reaction would produce a lower yield and purity of product (see, e.g., Declaration Under Rule 132 submitted with the December 4, 2003 Amendment).

Second, the acid starting product (VI) disclosed in Greenberg et al. is hardly purified ; as apparent from example 8c of Greenberg et al., the product of formula (IV) is isolated without purification. As a result, the starting product of the coupling reaction is not pure and this inevitably affects the yield and purity of the obtained product. By

contrast, according to the present invention, the starting product can be easily purified, thus facilitating the coupling reaction.

6. The process of the present invention presents the following unexpected advantages over that disclosed in Greenberg et al:

- yields are significantly higher;
- the obtained product is of higher purity; and
- the reaction can be easily carried out on an industrial scale as the starting product readily crystallizes, contrary to the starting product disclosed on Greenberg et al.

7. The undersigned Declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 09 day of August, 2004.

Denis Danvy  
Denis Danvy